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The effect of glycaemic control on neutralizing antibody response to COVID-19 among patients with Type 2 diabetes mellitus in the Kurunegala District of Sri Lanka; A prospective cohort study

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Abstract

Background:

The antibody response following COVID-19 vaccination among patients with diabetes mellitus (DM) is of particular concern given the increased risk of severe disease in this population. The correlation between glycaemic control among persons with DM and the antibody response was not published in Asian populations. Hence, this study aimed to determine whether glycaemic control has an association with the development of an adequate antibody response for SARS-CoV-2 among patients with DM following the administration of two doses of the COVID-19 vaccine.

Methods:

A prospective cohort study was carried out at three vaccination centers in the Kurunegala district from November 2021 to January 2022. Seventy-one patients with type 2 diabetes were recruited for this study and followed up on vaccination with the Sinopharm COVID-19 vaccine. HbA1c levels at the first dose and after 6-8 weeks from the second dose of vaccine were analyzed. The neutralizing antibodies (NAbs) were analyzed using C Pass™ neutralizing antibody detection ELISA Kit following 6-8 weeks of the 2nd dose.

Results:

The median (IQR) age of the total population (63.4% females) was 53 years (44.0-58.0) and they were diagnosed with diabetes for 6 years (3-11 years). The median first and second HbA1c values were 9.3% (7.2-10.7%) and 8.2% (7.1-10.2%) respectively. From the total population, only 66.2% developed protective levels of NAbs after 6-8 weeks of the second dose of the vaccine. The second HbA1c value was significantly lower compared to the first ($z=-2.63$, $p=0.008$). There was no significant difference in terms of sex, age, duration of diabetes, pre-vaccination HbA1c level, or HbA1c level 6-8 weeks after the vaccination among those who developed protective levels of antibodies and those who did not ($p>0.05$). There was no difference in sero-conversion depending on the abnormal HbA1c value (≥8%) (1st HbA1c $p=0.957$, 2nd HbA1c $p=0.360$).

Conclusion:

We did not detect an association between glycaemic control and sero-conversion. However, 1/3rd of patients with diabetes did not have a protective level of NAbs following 2 doses of Sinopharm COVID-19 vaccination. Furthermore, glycaemic control did not deteriorate with COVID-19 vaccination.

Keywords: COVID-19 Vaccine, Sero-conversion, Diabetes, Neutralizing Antibody

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused significant mortality and morbidity worldwide [1]. It is found that patients with both type 1 and type 2 diabetes are more susceptible to the severe illness of novel coronavirus disease (COVID–19). Previous studies have shown that patients with diabetes who had been vaccinated against Influenza and Hepatitis-B produced a reduced antibody response [2]. Nevertheless, the latest advancements in vaccine development have led to a significant improvement in their efficacy by mounting an improved immune response [3,4,5].

Both the World Health Organization and Centers for Disease Control and Prevention (CDC) have recommended vaccination of this vulnerable population, as these patients can develop severe disease if infected with SARS-CoV-2[3]. Protection against COVID-19 following vaccination is brought on by creating virus-specific neutralizing antibodies and a specific T cell-mediated immune response [6]. As of March 16th, 2022, more than 10 billion doses of different COVID-19 vaccines have been administered worldwide, including booster doses [7].

Patients with diabetes, particularly when combined with obesity, experience higher rates of infection and death caused by COVID-19. Most of this data is based on studies conducted on patients with type 2 diabetes[7]. Moreover, recent observations have shown that COVID-19 tends to be more severe in individuals with diabetes compared to those without diabetes, specifically when their blood sugar levels are poorly controlled with advanced age being a very prominent risk factor [7]. However, the effect of glycaemic control at the time of vaccination on these observations is yet to be explored in depth. HbA1c is a valuable parameter in monitoring glycaemic control in patients with diabetes[8]. Long-term sub-optimal glycaemic control, measured as HbA1c, is associated with higher mortality with COVID-19 [9].

If a protective anti-SARS-CoV-2 antibody response is not sufficiently induced in people with diabetes with suboptimal glycaemic control, the vaccination might provide a false sense of security, exposing them to infection at a higher rate. Sri Lanka had used many available vaccines for the public health vaccination campaign against COVID-19 which included inactivated vaccines such as Sinopharm and Sinovac. These contain the killed SARS-CoV-2 virus. It is known that the sero-conversion and T cell response is poor among people with diabetes following SARS-CoV-2 virus infection, especially among those with high blood glucose levels [10,11]. The same was reported following COVID-19 vaccinations [12], but data for the country, region, and the vaccines used in Sri Lanka are sparse. Our objective was to compare the seroconversion rate between people with optimal and sub-optimal glycaemic control following 2 doses of COVID-19 vaccination among patients with diabetes in the Kurunegala district.

Method

A prospective cohort study was conducted recruiting patients who were diagnosed with type 2 diabetes at the diabetic clinic in the Kurunegala district from November 2021 to January 2022 following ethical clearance from the ethics review committee of the faculty of Medicine, University of Kelaniya (Ref No: P/77/08/2021). A researcher visited the 3 vaccination centers closest to the Teaching Hospital Kurunegala where the patients were registered at the diabetic clinic. Consecutive eligible persons with type 2 diabetes who had come to get their first dose of the COVID vaccine were recruited after explaining the study. All the patients were recruited within a 2-week period at these centers. Informed written consent was obtained individually. Following data collection, a blood sample for HbA1c level was obtained at this 1st visit.

These patients were followed up to make sure that they get their second dose of vaccine as recommended (4 weeks from the 1st dose). All the registrants were asked to come to the diabetic clinic at the teaching hospital in Kurunegala for a follow-up at 6-8 weeks following the 2nd dose of the COVID vaccine (2nd visit). The second blood sample for HbA1c level and neutralizing antibodies were obtained at this visit. The laboratory investigations were carried out at the Faculty of Medicine, University of Kelaniya Sri Lanka.

The following inclusion and exclusion criteria were used for the study.

Inclusion criteria

-Age between 18 years to 60 years

-Diagnosed with type 2 diabetes for more than 12 months being followed up at the diabetic clinic in -Teaching Hospital Kurunegala.

Exclusion criteria

-Persons on treatment for malignancies or on immunosuppressive therapies

-People who had COVID-19 confirmed infection before or within the study period.

-Persons who had significant exposure to confirmed cases of COVID-19 and had been under 14-day quarantine within the previous 6 months.

History of chronic diseases including chronic kidney disease, liver diseases, and heart failure or HIV.

History of recent major surgery or trauma within one month.

The sample size for the survey was calculated assuming the following:

The proportion of persons with optimal and suboptimal control was hypothesized to be 33% using publications in Sri Lanka [13]. The difference in the proportion developing protective antibodies was hypothesized to be 0.3 between patients with diabetes who had optimal glycaemic control compared to those uncontrolled using publication reporting seroconversion of Hepatitis B[14] vaccination and Influenza vaccination[15]. The sample size calculation was done using Win Pepi. (PEPI-for-Windows, Version 11.65) which calculated a sample size of 69. We recruited 71 patients for this study[14].

Description of procedures

At the first visit (on the day of the first dose of vaccine administration), an investigator-administered questionnaire was used to obtain sociodemographic data and information regarding health status, duration of diseases, medications, previous history of COVID-19 infection and the type of COVID vaccine. Then, a 5ml venous blood sample was obtained by a trained phlebotomist under aseptic conditions using disposable equipment. This was used to analyze the HbA1c levels to measure the glycaemic control over the past 10-12 weeks. Blood samples were transported to the laboratories of the Faculty of Medicine on the same day to analyze HbA1c levels. A second blood sample (5ml) was obtained 6-8 weeks after the second dose of the vaccine for another HbA1c test and a serum sample for the investigation of neutralizing antibody assessment.

The neutralizing antibodies were detected using C Pass™ SARS-CoV-2 Neutralization Antibody Detection Kit. This is the only FDA/ EUA-authorized competitive ELISA test to detect neutralizing antibodies against SARS-CoV-2. This test has 100% specificity and 95% sensitivity for the detection of neutralizing antibodies against SARS-CoV-2. However, this is a qualitative test which indicates the presence or absence of a protective level of antibodies by the ELISA technique. This test is considered as the surrogate neutralization test which correlates to the gold standard plaque reduction neutralization assay. The test was performed at the Department of Medical Microbiology by a trained technician, under the supervision of an investigator, according to manufacturer guidelines. Blood was discarded within one month of testing.

Data Analysis

Data were presented as the median and interquartile range (IQR) as the age, duration of diabetes, and HbA1c values were not normally distributed. Chi-square tests were used for the analysis of categorical variables. The Wilcoxon signed-rank test was used to compare the 1st and 2nd HbA1c values. Mann Whitney U was used to analyze the dependent variables with seroconversion. Statistical tests were conducted in SPSS (IBM, version 28). GraphPad Prism version 9.3.1 (GraphPad Software Inc., San Diego, CA) and SPSS were used for generating graphs.

Results

Characteristics of the study population

Data was collected from 71 persons diagnosed with type 2 diabetes in the Kurunegala district. The majority (63.4%, n=45) were females. All the participants were vaccinated with the Sinopharm vaccine. The median age (IQR) of the population was 53 years (44.0-58.0). They were diagnosed with diabetes for a median of 6 years (3.0-11.0). The median HbA1c value at the first visit before vaccination was 9.3% (7.2-10.7) and the 2nd HbA1c value was 8.2% (7.1-10.2).

When the HbA1c values were compared pairwise using Wilcoxon signed rank test, the second value was significantly lower compared to the first ($z=-2.631$, $p=0.008$) (Table 1). When the persons with HbA1c values <8% and ≥8% were compared, the time since diagnosis of DM was significantly lower among those with lower/normal HbA1c values ($p=0.004$) (Table 1).

Seroconversion following Sinopharm vaccination and glycaemic control.

Only 66.2% of the total population developed protective levels of antibodies 6-8 weeks after the second dose of the Sinopharm vaccine. There was no difference in sero-conversion depending on the level of HbA1c value of ≥8% compared to <8% (1st HbA1c $p=0.957$, 2nd HbA1c $p=0.360$) (Table 1). The proportion of persons who developed protective antibody levels in the two sexes was comparable ($p>0.05$).

Comparison of sero-converted with non-seroconverted population.

There was no significant difference in the median age among those who developed adequate antibody

Table 1: Characteristics of persons with <8% and >8% HbA1c values at the first vaccination.

	HbA1c <8% n=21		HbA1c ≥8% n=50	
	n	%	n	%
Males	7	9.9	19	26.8
Females	14	19.7	31	43.7
Seroconversion	14	19.7	33	46.5
	median	IQR	median	IQR
Age	52.0	45.0-57.5	53.0	43.0-59.0
Time since diagnosis of DM*	3.0	1.00-8.0	8.0	3.0-16.0
2nd HbA1c*	6.8	6.1-7.1	9.3	7.9-10.7

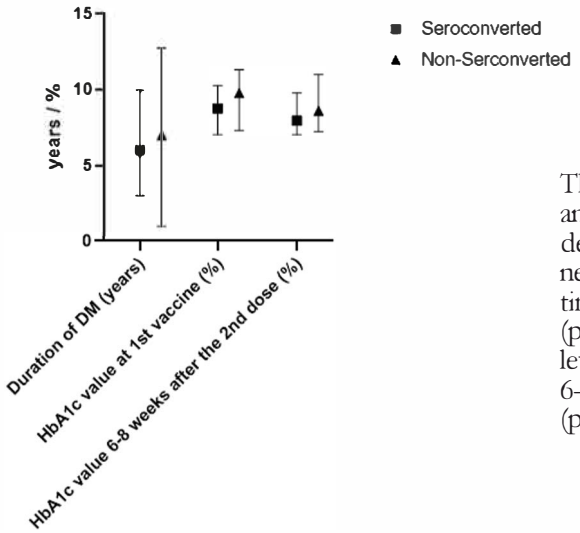
* Significantly different using MWU p<0.01

response and those who did not [52.0 years (44.0-59.0) vs 54.0 (44.0-57.7) MWU=526.5, p=0.648 respectively]. Time since diagnosis of diabetes [6.0 (3.0-10.0) vs 7.0 (1.0-12.7) MWU=540.5, p=0.774], the pre-vaccination HbA1c level [8.8 (7.1-10.3) vs 9.8 (7.4 - 11.3), MWU=467.5, p=0.241] or the HbA1c level 6-8 weeks after the vaccination [8.0 (7.1 - 9.8) vs 8.6 (7.3 - 11.0), MWU=464.5, p=0.226] were not significantly different between the seroconverted group and the group who did not (Figure 1). When both HbA1c values were plotted among the seroconverted population and those who did not, the correlation coefficients were comparable (z=-0.326, p=0.744) (Figure 2). The model was non-significant in regression analysis when the age, time since diagnosis of DM, sex, and HbA1c values were used to ascertain the likelihood of seroconversion among persons with diabetes $\chi^2(7)=5.6$, p>0.05.

Discussion

The current study highlights the importance of checking the protective antibody development after vaccination in high-risk populations, as we found that 33.8% of persons with type 2 diabetes did not develop adequate levels of antibodies in our study population.

In addition, we noted that the age, time since diagnosis of diabetes, and glycaemic control did not determine the sero-conversion measured as developing protective level of NAbs. The HbA1c values when compared in each individual showed a better control with the repeated assessment. This is contradicting previous reports where vaccination has caused derangement in glycaemic control. It could also be possible that the patients took extra precautions since they were being vaccinated and were motivated for better glycaemic control as they were recruited for this study assessing HbA1c levels.



There were no significant differences among the group with diabetes who developed protective levels of neutralizing antibodies with regards to time since diagnosis of diabetes (p=0.774), the pre-vaccination HbA1c level (p=0.241), or the HbA1c level 6-8 weeks after the vaccination (p=0.226)

Figure 1 : Characteristics of the diabetic population who seroconverted compared to those who did not.

The immune response following SARS CoV-2 Infection and vaccination

While innate immune responses are responsible for blocking the entry of viruses into cells, the adaptive responses are important for viral clearance by antibody-mediated and T cell-mediated responses, in addition to providing a long lasting memory response [15]. The role of the adaptive immune response following vaccination and natural infection with SARS CoV-2 is well characterized in several studies [3,16,17,18,19].

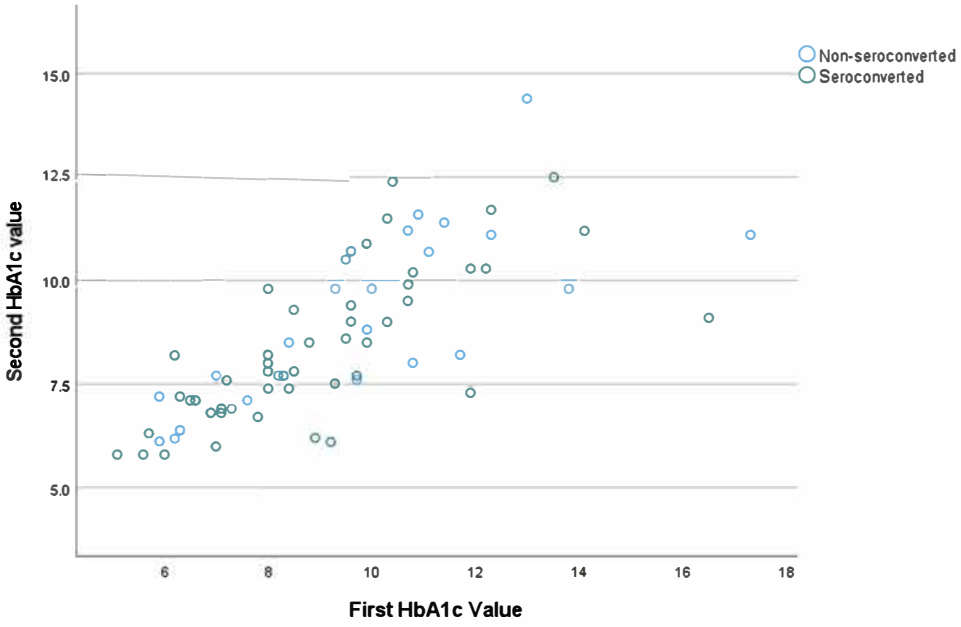
Both the mRNA and vector vaccines which are approved for COVID-19, encode the spike (S) protein of the SARS-CoV-2, which is the primary target for neutralizing antibodies generated from natural infection and vaccination [19]. These vaccines have proven to produce a good neutralizing antibody response and T-cell response [19,20]. Although approved by WHO much later, there are other types of COVID vaccines such as Sinopharm and Sinovac which contain the killed SARS-CoV-2 virus, and Novovax and Sinofi/GSK which contain proteins from the SARS-CoV-2 virus.

Although there are many studies which have compared the immune response of the earlier approved vaccines in both immune-competent and immune-compromised patients [17,19,20,21], the studies which are done to find out the efficacy of other vaccines such as Sinopharm and Sinovac are sparse. A study conducted in Sri Lanka has reported high sero-conversion rates of 95% with the Sinopharm vaccine where comorbidities were not evaluated separately. Jeewandara et al also reported that the levels were similar to convalescent sera making Sinopharm as effective as SARS-CoV-2 infection in producing antibodies. The T cell and B cell responses which were generated by the vaccine were reported to be less than other vaccines and although the T cell response remained stable over 3 months, the antibody levels declined. Hence, we assume that our time frame for measuring antibodies at 6-8 weeks following vaccination would have captured optimal seroconversion [22].

Humoral immune responses in patients with diabetes are thought to be defective due to several mechanisms [26,27]. The neutralizing antibody response thus would be compromised in the diabetic population. Studies done so far indicate improved glycaemic control to be a factor affecting vaccine responsiveness [12,28]. Soeted-jo et al., in their systematic review, managed to cover eight studies with a total of 64468 patients and 5156 patients with diabetes. The vaccines included were the BNT162b2 vaccine (Pfizer/BioNTech), CoronaVac (Sinovac Life Sciences), Covishield™ (ChAdOx1-nCOV), and Covaxin™ (BBV-152). The effectiveness results showed lower seropositivity and antibody responses following vaccination in patients with diabetes than in healthy controls [28].

Glycaemic control and SARS-COV-2

A study conducted in India in patients after diagnosis of SARS-COV-2, those who were seronegative had higher HbA1c levels and longer duration of diabetes [10]. However, two studies conducted in Italy found that patients with DM had an almost similar humoral



There were no significant differences in the correlation in HbA1c values among those who sero-converted compared to those who did not. (z -0.326, p=0.744).

Figure 2 : Comparison of the HbA1C values depending on seroconversion

response to those without DM in terms of antibody titers [29,30]. As we did not compare the antibody development in normal persons taking the same vaccine, which was a limitation due to limited funding and the time schedules of vaccine rollout, we could not make the comparison.

HbA1c is used to monitor glycaemic control for the previous 10-12 weeks, therefore, it is attributed to be affected by the more recent blood glucose levels[7]. It is identified as being a better predictor of complications [31]. It would be crucial to identify the relationship between glycaemic control and the development of a protective antibody response following vaccination as the inability to produce a protective anti-SARS-CoV-2 antibody response among those with diabetes, as we have shown in this study, would be detrimental to the public health response to prevent morbidity and mortality from SARS-COV-2. The glycaemic control is reported to be worsened after infection with SARS-COV-2, and COVID-19 vaccination in type 2 diabetes treated with oral hypoglycaemic medications and insulin [32]. We were able to establish that the vaccination in fact did not deteriorate the HbA1c values.

There is limited published data available on prospective studies regarding the development of immunity among diabetes patients following COVID-19 vaccines especially with the inactivated vaccines [33]. The correlation of glycaemic control with the development of the humoral immune response has not been clearly established. In the CAVEAT study, it was highlighted that the immunological response is adversely affected by hyperglycemia at the time of vaccination, and achieving adequate glycaemic control after the vaccination improves the immunological response [12]. SARS-CoV-2 BNT162b2 mRNA-based vaccines elicited a weaker immune response after the first dose in patients with DM compared to persons without DM where approximately 17% did not develop protective levels of antibodies compared to 9% in non-diabetic persons. The second dose increased the level of protective antibodies in patients with diabetes to 96.4% [34]. The differences we report in the current study could be due to the differences in the vaccine used and the population characteristics. Currently, there is no recommendation to check glycaemic control before vaccination, but those with diabetes will be prioritized for vaccination. As reported by the previous studies, the level of cellular immunity and antibody development following vaccination may be altered by hyperglycemia although we could not find a correlation between the glycaemic level at the time of vaccination and seroconversion.

Although the results of this study can be applied to the Sri Lankan population, caution should be exercised when applied to regions with socioeconomic or ethnic differences. We acknowledge that enrollment of a non-diabetic control population would have made the comparison with the normal population possible in addition to glycemic control within the population with DM. We emphasize the need for national health research bodies to set up protocols for research and auditing that would come into effect automatically, in preparation for a similar situation as the COVID-19 pandemic.

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